EXHIBIT 42

Interpretation of Epidemiologic Studies on Talc and Ovarian Cancer

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Executive Summary

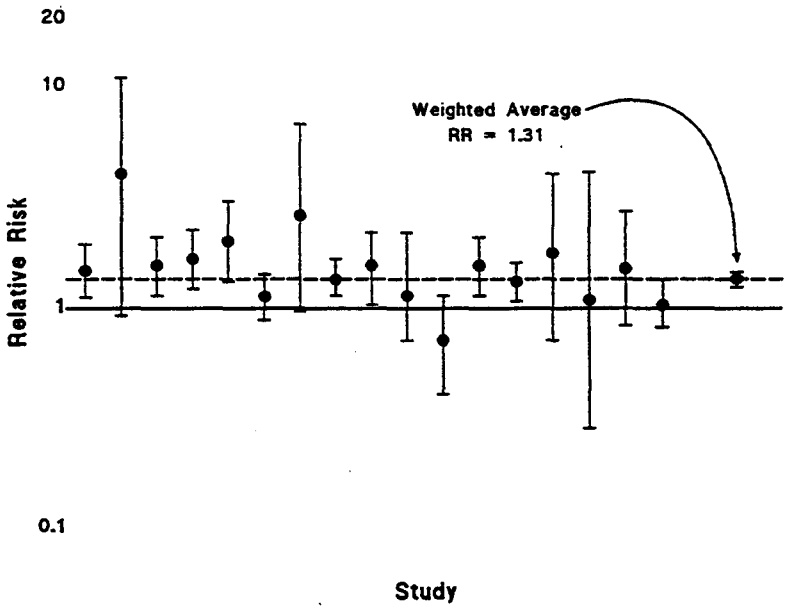
A weighted average of the results from epidemiologic studies to date measuring the relation between talc and ovarian cancer risk gives an overall relative risk of 1.31, with a 95% confidence interval of 1.21–1.41. Bias and causation are competing explanations for the weak positive association observed. This weak association could be an underestimate of a stronger association if there are errors in measuring talc exposure that apply uniformly to all study subjects (nondifferential misclassification). On the other hand, nondifferential misclassification does not bias an association that is null to begin with, so postulating nondifferential misclassification cannot shed light on whether the association results from a causal relation or not. Most of the published studies are interview-based case-control studies, subject to recall bias, which can readily give rise to associations of this magnitude. The evidence from these studies regarding recall bias is mixed. Uncontrolled confounding can also easily explain associations this weak; although no single confounding factor would seem to account for the overall effect, the combined effect of several such unidentified confounders could do so. In considering these competing explanations of bias and causation, the evidence in favor of a causal explanation is only the overall weak association of a relative risk of 1.31. The lack of a plausible biologic mechanism, on the other hand, weighs against a causal interpretation. Also weighing against a causal explanation is the dose-response pattern among talc users, which is an inverse trend for both duration of use and frequency of use. A causal relation would predict a positive trend, not an inverse trend. Based on these considerations, we suggest that the evidence to date does not indicate that talc can be "reasonably anticipated to be a human carcinogen."

Introduction

In this document we offer an interpretation of the epidemiologic literature with respect to the causal hypothesis that talc exposure causes an increase in the occurrence of ovarian cancer. Overall, we identified 23 epidemiologic studies conducted since 1980 that have examined consumer talc exposure with respect to subsequent risk for ovarian cancer.[1-23] The search methodology is described in the appendix. Sixteen of these were case-control studies reporting new data with effect estimates for talc exposure,[2-5,7,10,11,13-15,17-19,21-23] and one was a cohort study reporting an effect estimate.[9] One study examined occupational exposure to talc in women, but there were few exposed women in this study[16]; the other studies did not report quantitative effect estimates. The importance of this comparatively small set of epidemiologic studies is underscored by the paucity of relevant animal research on this question.

Most of these published reports come from epidemiologic studies in which talc was not the primary focus. Perhaps for this reason, talc exposure information was often crude. In only a few of these studies was there any attempt to categorize talc exposure by frequency of use or duration of use. For the 17 studies that reported some epidemiologic measure of effect, it was usually a relative risk estimate for ovarian cancer given that there was some exposure to talc, compared with no exposure or minimal exposure. These results are depicted graphically in figure 1. The findings on balance indicate a slight positive association between talc exposure and ovarian cancer, with an overall weighted relative risk of 1.31, and a 95% confidence interval of 1.21–1.41.

Figure 1
Study-specific Relative Risk Estimates for Ovarian Cancer Among Talc Users, and Overall Weighted Average of Study Results



Issues Affecting Causal Inference

Inferring a causal relation from a pattern of epidemiologic results follows no recipe, but certain principles can be applied. To begin with, what alternative explanations might be offered to explain a pattern of positive findings? If an uncontrolled confounding factor or a study-related bias could explain the results, a causal inference is less reasonable. Second, is there a plausible biologic mechanism? For example, environmental tobacco smoke shows a weak association with lung cancer in numerous epidemiologic studies of never smokers, but the plausibility of the relation, based on the known constituents of the smoke and their effect in higher concentrations, among active smokers, makes a causal inference more reasonable. Third, is there a consistent dose-response trend in the data? With rare exception, every causal relation in epidemiologic research shows a progressive relation between various measures of increasing exposure. In this discussion paper, we address the following issues that we believe are potentially relevant to causal inference regarding talc and ovarian cancer:

1. Exposure misclassification
2. Recall bias
3. Confounding
4. Dose-response trends
5. Biologic mechanism

Below we discuss briefly the import of each of these topics with respect to the interpretation of the epidemiologic literature of talc and ovarian cancer. We omit discussion of the role of chance in explaining any of the findings, because the combined weight of the 17 studies in figure 1 indicates that chance alone is an unlikely explanation for the overall weighted average of relative risks from the studies of 1.31. Other possible issues, such as selection biases and reverse causation might be relevant, but appear less important to us in interpreting these results, so we have omitted them in the interests of brevity. (Reverse causation, for example, could occur if preclinical ovarian cancer prompted women to use talc; while this situation is possible in some instances, we do not think it is a realistic explanation for the observed effects.)

Exposure Misclassification

Nearly all the studies were case-control studies. It is commonly believed that the validity of case-control studies is worse than that of cohort studies, but this view is mistaken. The validity of a study depends on the specifics of the study design, the nature of the data, and the nature of the hypothesis that the study addresses. For example, a cohort study that examines the long-term risk of cancer among coffee drinkers after a one-time dietary assessment of coffee consumption would suffer from weak exposure assessment. Although the exposure information might be accurate for the time at which it was collected, the exposure status of cohort members will change with time and the initial measure might be only poorly correlated with a more meaningful measure of coffee consumption. The effect of having a poor measure of exposure will be considerable nondifferential misclassification, a type of error that introduces a bias into study results that tends to drive effect estimates towards the null condition of no effect. In contrast, it may be possible to get more detailed exposure information from study subjects in a case-control study, which might thus avoid some of the bias that would result from a cohort study.

Much like coffee consumption, talc exposure is likely to vary over time as women age and their reasons for deciding to use talc change. Consequently a single baseline assessment of talc exposure at the start of follow-up in a cohort may lead to effect estimates that are biased toward the null. If talc habits are steady over time, a single baseline assessment becomes more informative. Furthermore, if talc use influences cancer risk with a long induction period, talc assessment at the start of a cohort study is more meaningful than an assessment of coffee drinking on heart disease risk, which is thought to have only a short-term effect.

Case-control studies also suffer from exposure misclassification, but the potential exists to extract more detailed history of exposure from the subject interview. In most of these studies, the exposure metric is based on interview information. It is subject to inaccuracies from recall error, as well as inaccuracies reflecting the nature of the questions asked and their relation to any biologically relevant measure of talc exposure. Ideally one would wish to have a measure of talc dose within the upper reproductive tract. The actual measures obtained by interview, however, are likely to be only modestly correlated with a hypothetically ideal measure. The result of this inevitable non-differential misclassification would be to bias any real effect towards the null. Nevertheless, one cannot draw the conclusion that the overall slight positive relation between talc exposure and ovarian cancer must be an underestimate of a larger effect because of nondifferential misclassification. Non-differential misclassification does not introduce any bias toward the null if the association is null to begin with, so to draw the conclusion that the overall effect estimate from the 17 studies is an underestimate, one must already know or assume that there is an even stronger positive relation in the data. Thus, the prospect of non-differential misclassification in measuring talc exposure does not provide any help by itself in assessing whether talc is related to ovarian cancer.

Recall Bias

Cohort studies do not suffer from recall bias, but recall bias is an issue for case-control studies that obtain exposure information from subject interviews. Such was the case for all the case-control studies whose effects are summarized in figure 1. Recall bias can readily introduce enough bias to produce the modestly-sized overall effect (RR = 1.3) that emerges from these studies. As an example, one of us reported an association between Bendectin and congenital heart disease in 1979, with a RR of 1.6.[24] One possibility for that positive relation was recall bias, a strong consideration in light of the study design that produced the finding (the study was not designed to evaluate Bendectin, which was only an incidental finding). To resolve the issue, a second study was undertaken, this time aimed at evaluating an effect of Bendectin by eliminating recall bias using a different design.[25] The second study found a RR of 1.0, prompting the conclusion that the RR of 1.6 reported in the earlier study was due to recall bias. The amount of recall bias for Bendectin in the 1979 study amounted to an apparent effect that was much stronger than the overall effect estimate for talc and ovarian cancer in the combined studies in figure 1.

We believe that there is mixed evidence for recall bias in these studies. We base this interpretation on the few studies that examined the effect of talc separately among women who had a tubal ligation and those who did not. If recall bias were the explanation for the full effect seen in the published literature, we would predict that the effect of talc exposure would appear to be about the same for women who have a tubal ligation and those who did not, because tubal ligation is unlikely to affect recall bias. In contrast, it would likely affect any biologic action of

talc. Only three studies give information relevant to this question. In those studies, the evidence is mixed. In one study the effect of talc is greater among women who have not had a tubal ligation,[22] and in a second, talc use appeared to have no adverse effect among women who had either a hysterectomy or a tubal ligation.[23] In the third study,[2] however, there was little difference in the effect of talc for women with and without tubal ligation or hysterectomy and the effect for both groups was near null. Thus, the overall evidence on the possibility of recall bias is equivocal, with no clear answer as to whether recall bias can be eliminated as an explanation.

Confounding

Although there are some strong risk factors for ovarian cancer, for any of them to be confounding to an extent that could account for the positive relations that have been reported, they would have to be strongly correlated with talc use. Family history, ethnicity, obesity and some reproductive risk factors are positively associated with the risk of ovarian cancer, but the magnitude of these associations does not appear high enough to introduce enough confounding, even jointly, to explain completely the positive association. Of course, it remains possible that yet unidentified risk factors for ovarian cancer could be important confounders, and several such factors in the aggregate could give risk to an overall association as weak as the one between talc and ovarian cancer.

Dose-response trends

A nearly constant feature of causal relations in epidemiology and in the pathogenesis of cancer in particular is a monotonically increasing relation between measures of exposure and disease risk. Even when disease risk increases through a threshold phenomenon, progressive dose-response trends are observed because the exposure measure varies and smooths the step relation of a threshold into a gradual climb in risk. In contrast, many biases would not produce a monotonic dose-response relation. For example, Horwitz and Feinstein advanced a theory of "detection-bias" as a non-causal alternative to the theory that exogenous estrogens cause endometrial cancer.[26] According to this theory, administration of estrogens would provoke genital bleeding among some women, leading to a work up and to the diagnosis of pre-existing endometrial cancers, accounting for the observed association. This theory, however, predicted that the increase in endometrial cancer risk would be greatest for short-term users of exogenous estrogens and would decline toward no effect for longer-term users. In actual fact this inverse dose-response trend was not observed, undermining the detection bias theory.

Exposure to talc can be characterized by the age at which use started, the number of years of use, and the frequency of use (e.g., number of times per day or per week). Among the talc studies, several reported on either frequency of talc use or duration of talc use, or both. We combined the findings from these studies into a meta-regression,[27] an analysis that combines dose-specific information from various studies into a single weighted regression analysis. Each data point in a meta-regression represents one effect estimate at a given dose level; the data points are weighted by the precision of each estimate, back-calculated from the confidence interval for that estimate.

In figure 2 we show the data points and meta-regression line for frequency of talc use, and in figure 3 for duration of talc use. These regression analyses confirm the picture that one obtains from reading the individual studies (table 1): the dose-response relation across dose levels above zero for talc exposure is not increasing, but instead declines. Although

misclassification could flatten a dose-response curve, it would not produce an inverse dose-response curve. Thus, the observed pattern, whether based on individual studies or from the combined meta-regression analysis, is not consistent with a causal interpretation for talc exposure. Instead it suggests that some as yet unidentified bias accounts for the overall modest relation between talc exposure and ovarian cancer.

Figure 2
Trend in Relative Risk by Frequency of Talc Use Among Users

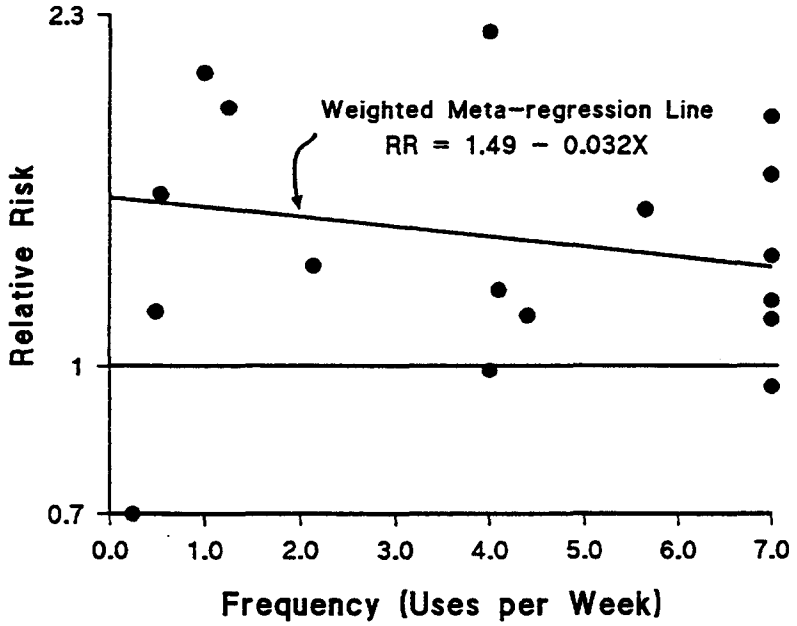


Figure 3
Trend in Relative Risk by Duration of Talc Use Among Users

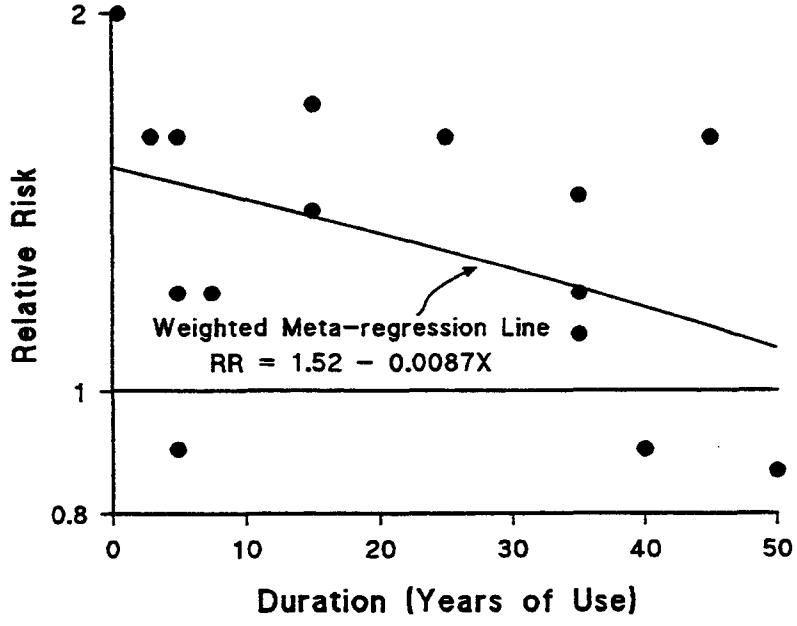


Table 1
Relative Risk Estimates of Ovarian Cancer by Frequency and Duration of Talc Use*

Citation	Frequency (Applications/wk)	Relative Risk	95% Confidence Interval
Booth et al.1989	7.00	1.30	0.80-1.90
	1.00	2.00	1.30-3.40
	0.25	0.70	0.30-1.80
Chang and Risch 1997	1.25	2.00	1.24-2.73
	4.40	1.13	0.74-1.72
	7.00	0.95	0.61-1.49
Cramer et al. 1999	4.00	2.21	1.37-3.56
	7.00	1.17	0.78-1.76
	7.00	1.57	0.80-3.10
Gertig et al. 2000	0.50	1.14	0.81-1.59
	4.00	0.99	0.67-1.46
	7.00	1.12	0.82-1.55
Harlow et al. 1992	0.55	1.50	0.80-2.70
	4.10	1.20	0.60-2.20
	7.00	1.80	1.10-3.00
Whittemore et al. 1988	2.14	1.27	0.82-1.96
	5.65	1.45	0.94-2.22

Citation	Duration (years)	Relative Risk	95% Confidence Interval
Chang and Risch 1997	15	1.70	1.09-2.64
	35	1.44	0.96-2.15
	50	0.86	0.54-1.38
Harlow et al. 1992	5	1.20	0.50-2.60
	25	1.60	1.00-2.70
	45	1.60	1.00-2.70
Ness et al. 2000	1	2.00	1.00-4.00
	3	1.60	1.10-2.30
	7.5	1.20	0.80-1.90
	35	1.20	1.00-1.50
Whittemore et al. 1988	5	1.60	1.00-2.57
	35	1.11	0.74-1.65
Wong et al. 1999	5	0.90	0.60-1.50
	15	1.40	0.90-2.20
	40	0.90	0.60-1.20

* For Open-ended Categories, the Values Assigned Assume that the Upper Category Boundary Corresponds to a Maximum Frequency Equal to Daily Use and a Maximum Duration of Use of 60 Years

Biologic Mechanism

The most plausible biological mechanism relating to the development of ovarian cancer concerns ovulation and the hormonal factors affecting it. Specifically, factors that suppress ovulation, such as gravidity, breast feeding, oral contraceptive use, tubal ligation and hysterectomy appear to reduce strongly the risk of ovarian cancer. Body mass index may also affect ovarian cancer risk. Medical conditions that may affect ovulation and also appear to increase the risk of ovarian cancer include endometriosis, ovarian cysts, and hyperthyroidism.

It does not appear plausible, however, that talc exposure has a direct effect on ovulation. If talc exposure is correlated with factors that affect ovulation, that correlation would produce confounding, as discussed above. If talc were a cause of ovarian cancer, it is presumably through a different mechanism than the many risk factors already known to affect ovarian cancer risk. There is no other evidence regarding such a mechanism, nor any clear evidence that talc applied perineally or on diaphragms makes its way physically to the ovaries. Ness et al suggest that inflammation may mediate ovarian cancer risk and that talc may play a role by causing inflammation.[17] This theory merits further investigation, although the tenability of the theory rests on the issue of whether talc particles physically reach the ovaries. Without a clear biologic mechanism for talc to cause ovarian cancer, an inference that talc does cause ovarian cancer would be an example of a "black-box" inference, meaning that the inference lacks a biologic foundation. "Black-box" inferences, such as the inference some draw that electromagnetic fields increase the risk for various cancers, are not necessarily invalid, but they are inherently more tenuous than inferences that are rooted in biologic explanations.

Conclusion

The only evidence to support a causal interpretation is the overall modest positive association seen in most of the epidemiologic studies that we have cited. The association is weak enough to be plausibly explained by unidentified bias. Recall bias is one possibility, but unidentified confounding could also readily give rise to the weak level of association that confronts us from these studies. Bias and causation are competing explanations for the weak positive association observed, an association that could be an underestimate of a stronger real association if nondifferential misclassification has diluted it. In considering these competing explanations, the lack of a plausible biologic mechanism based on the evidence to date weighs against a causal interpretation. More important, there is also positive evidence against a causal association: the inverse dose-response trend for both duration of use and frequency of use, a pattern that could not be explained by a causal relation. Based on these considerations, we suggest that the evidence to date does not indicate that talc can be "reasonably anticipated to be a human carcinogen."

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Appendix

Literature Search Methodology

The literature search was designed to find published epidemiologic studies specifically relating to the perineal use of non-asbestiform talc. The 2000 NTP Draft Report was used as the initial resource to locate applicable studies. To identify other relevant publications, an on-line search was performed in Dialog and using the internet. In addition, medical and scientific resources such as Medline, Toxline, and SciSearch were queried using various keyword terms including "talc," "non-asbestiform," "ovarian cancer," and "perineal." The search was limited to papers published after 1980, because asbestiform products were removed from the market in 1976. Once relevant articles were obtained, bibliographies were "tree-searched" to identify other applicable studies that may have been omitted during the on-line search. "Tree-searching" involves reading an article's bibliography, and then identifying citations that may contain appropriate information based on the title or author. "Tree-searching" identified early studies or those not recorded in on-line databases.